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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,423	04/03/2001	Patricia C. Weber	ID01152	2057

24265 7590 03/07/2006

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,423	WEBER ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,7 and 9-17* is/are rejected.

7)☒ Claim(s) *1-3 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

2. Claims 1-5 and 7-17 are pending in the application.

3. Applicant's amendment to the claims, filed on 12/14/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

4. Receipt of a substitute specification, filed on 12/14/2005, is acknowledged.

5. Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, and a statement of their sameness, all filed on 12/14/2005, is acknowledged.

6. Receipt of an information disclosure statement, filed on 12/14/2005, is acknowledged.

7. Applicant's arguments filed on 12/14/2005 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

8. The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

9. All references cited in the information disclosure statement filed on 12/14/2005 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Compliance with Sequence Rules

10. The sequence listing, filed in computer readable form (CRF) and paper copy on 12/14/2005, fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). There is no amendment directing entry of the sequence listing into the specification and there is no statement that the content of the paper and CRF copies include no new matter. Appropriate action is required.

Claim Objections

11. Claims 1, 4, 9, 11-12, and 16 are objected to as reciting an improper alternative expression. See MPEP § 2173.05(h). Regarding claims 1, 9, 11-12, and 16, it is suggested that the alternative expression be amended to recite, *e.g.,* "selected from the group consisting of SEQ ID NO:3…and SEQ ID NO:17" or "selected from the polypeptide defined by…SEQ ID NO:3…or SEQ ID NO:17." Regarding claims 4, 9, and 12, it is suggested that the alternative expression be amended to recite, *e.g.,* "the amino acid substitution is selected from the group consisting of Asp 73 and Arg 81" or "the amino acid substitution is selected from Asp 73 or Arg 81." Appropriate correction is required.

12. Claim 10 is objected to because of the recitation of "HCV." Abbreviations should not be recited in the claims without at least once reciting the entire phrase, i.e., "Heptatitis C Virus" for which the abbreviation is used. Appropriate correction is required.

13. Claim 17 is objected to as being grammatically incorrect in the recitation of "the polypeptides defined by..." It is suggested that the plural "polypeptides" in the aforementioned phrase be amended to the singular "polypeptide."

Claim Rejections - 35 USC § 112, Second Paragraph

14. Claims 4-5, 7, and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 4-5, 7, and 12-14 are drawn to variants of SEQ ID NO:3, 5, 6, or 17 or crystals thereof and are dependent upon claims 3 and 11, which are drawn to SEQ ID NO:3, 5, 6, or 17 or crystals thereof. Claims 4-5, 7, and 12-14 are confusing in that it is unclear as to how a polypeptide can be SEQ ID NO:3, 5, 6, or 17 (claim 3 or 11) and simultaneously be a mutant thereof (claims 4-5, 7, 12, or 13). It is suggested that applicant clarify the meaning of the claims.

b. Claims 5 and 13 are confusing in that the recited substitutions at positions 73 (lysine or arginine for aspartate) and 81 (glutamate or aspartate for arginine) are not non-polar as required in claims 4 and 12, respectively, as evidenced by Voet et al.

["Biochemistry, Second Edition," Voet and Voet, John Wiley and Sons, New York, 1995, p. 59]. It is suggested that applicant clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

15. Claims 4-5, 7, 9, and 12-14 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims have been amended to alter specific amino acid positions and/or a particular sequence identifier. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description." The examiner can find no showing of support in the instant response in accordance with MPEP § 2163 for the recited limitations. It is suggested that applicant show support for the limitations at issue.

16. The written description rejection of claims 10-17 under 35 U.S.C. § 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the rejection is overcome by claim amendment.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to adequately describe the genus of small molecule HCV helicase inhibitors (claim 10), crystalline compositions (claims 11-15), precipitant solutions of claim 16, and buffered solutions of claim 17.

Regarding the genus of small molecule HCV helicase inhibitors, as noted in the prior Office action:

> The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).
>
> The instant specification does not disclose the identity of a specific HCV helicase inhibitor. Some HCV helicase inhibitors are known in the art, however, these species do not represent the entire genus of HCV helicase inhibitors, and Applicants have not disclosed the common structural characteristics of species in the instant genera of HCV helicase inhibitors that correlate to their function. One of skill in the art would be unable to predict either the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of molecules are not adequately described.

The recited genus of small molecule HCV helicase inhibitors encompasses widely variant species, including any "small" molecule HCV helicase inhibitor having any structure and the known representative species fail to reflect the variation among

members of the genus. At least for these reasons, the specification fails to describe all members of the recited genus of small molecule HCV helicase inhibitors.

Regarding the claimed genus of crystalline compositions, it is noted that while the structures of the polypeptides of the crystals is adequately described, the structure of the crystal itself is not. At the time of the invention, it was well-known in the art that the structure of a protein crystal was defined by three repeating vectors a, b, and c, with angles α, β, and γ, between them. See pp. 586 and 2725 of the "Encyclopedia of Molecular Biology" (Creighton, T., John Wiley and Sons, Inc. New York, 1999). In the instant specification, a protein crystal of SEQ ID NO:17 is described that has space group $P2_1$ and unit cell dimensions a=34.8 Å, b=67.1 Å, c=58.4 Å, $\alpha=\gamma=90°$, $\beta=101.3°$. Other than this single disclosed species, the specification fails to describe any other crystals as encompassed by the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." The structures of the claimed crystalline compositions are unlimited with respect to space group and unit cell dimesions, and thus encompass widely variant species. The single disclosed species fails to adequately describe all crystalline compositions as encompassed by the claims.

Regarding the genus of claimed precipitant solutions and buffered solutions of claims 16-17, the solution of claim 16 includes a genus of precipitant compounds, salts, buffers, and protein stabilizing agents and the solution of claim 17 includes a genus of

protease inhibitors. Each respective genus encompasses widely variant solutions, having any precipitant compounds, any salts, any buffers, any protein stabilizing agents, and any protease inhibitor. The specification discloses only a single representative species of a precipitant solution, *i.e.,* 100 mM MES, pH 5.4, 20% MPD, 5 mM DTT at 4 degrees Celsius (specification at p. 43, l. 11-14), and only a single representative species of protease inhibitor for a buffer solution, *i.e.,* AEBSF (specification at p. 35, l. 6). These single disclosed species fail to adequately describe all precipitant solutions and buffered solutions as encompassed by the claims.

Given the lack of description of a representative number of protein crystals, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

17. The scope of enablement rejection of claims 10-17 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the rejection is overcome by claim amendment.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification in view of the prior art fails to enable a skilled artisan to make and/or use the claimed invention without requiring undue experimentation. The claims are so broad as to encompass a polypeptide of claim 1 in complex with any small

molecule HCV helicase inhibitor (claim 10), a crystalline composition having any space group and unit cell dimensions as encompassed (claims 11-15), a precipitant solution having any precipitant compounds, any salts, any buffers, and any protein stabilizing agents, wherein the claim recites a broad range of concentrations for the recited components (claim 16) and a buffer solution comprising any protease inhibitor and a broad range of concentrations for the recited components (claim 17).

Regarding the small molecule HCV helicase inhibitor having any structure, the specification fails to provide sufficient guidance for making *all* small molecule inhibitors as encompassed by the claims. While methods for screening a polypeptide for inhibitors thereof were known at the time of the invention, the specification provides no guidance for making all small molecules with an expectation that the resulting molecule will have the ability to inhibit HCV helicase, and a significant amount of experimentation is required to identify all small molecule inhibitors as encompassed by the claims.

Regarding the crystalline compositions having any space group and unit cell dimensions as encompassed of claims 11-15, the state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al.

("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). In this case, the specification teaches only a single working example of a crystalline composition and method for making, *i.e.,* the crystal of SEQ ID NO:17 as disclosed at pp. 41-42 of the specification. Other than this single working example, the specification fails to provide guidance for making other diffraction-quality protein crystals of the polypeptides encompassed by the claims and, as evidenced by the references cited above, a skilled artisan has no expectation that such crystals can be produced.

Regarding the precipitant and buffer solutions of claims 16-17, the specification discloses the use of such solutions for crystallization and NMR studies, respectively (specification at pp. 18 and 22) and discloses only a single working example of each solution that is useful for practicing NMR or protein crystallography (specification at pp. 35 and 43) and provides no guidance for altering the each of the solutions with an expectation of maintaining the desired utility. Further, regarding the precipitant solution, it is well-known in the prior art that even slight variations in a crystallization buffer can

significantly affect the ability to obtain diffraction-quality crystals. See Branden et al. (*supra*), which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle) and Wiencek (*Ann Rev Biomed Eng* 1:505-534), which teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). Also, regarding the buffered solution of claim 17, it is noted that the specification fails to provide sufficient guidance for making *all* protease inhibitors as encompassed by the claims. While protease inhibitors were known at the time of the invention, the claims are not so limited and a significant amount of experimentation is required to make all protease inhibitors as encompassed by the claims.

At least for these reasons, undue experimentation is required for a skilled artisan to make and/or use the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

18. Claim 15 is rejected under 35 U.S.C. § 102(b) as being anticipated by Kim et al. [(1998) *Structure* 6:89-100; cited in the PTO-892 attached to the 6/14/2005 Office action]. Claim 15 is drawn to a crystalline composition comprising a polypeptide "described by" the structural coordinates of Table 5.

Initially, it is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." Claim 15 is

drawn to a crystalline composition of an isolated polypeptide "described by" the structural coordinates of Table 5. Webster's dictionary defines the term "describe" as "to represent," thus, the examiner has broadly interpreted an isolated polypeptide "described by" the structural coordinates of Table 5 as not being limited to the sequence of amino acids as set forth in Table 5, but a polypeptide that is "representation" of those structural coordinates.

Kim et al. teaches a crystal of HCV NS3 RNA helicase (see particularly p. 98). This anticipates claim 15 as written.

Conclusion

19. Status of the claims:

Claims 1-5 and 7-17 are pending.

Claims 4-5, 7, and 9-17 are rejected.

Claim 1 is objected to and claims 2-3 and 8 are objected to as being dependent upon an objected claim.

Claims 1-5, 7-14, and 16-17 would be allowable if rewritten to overcome the objection and rejection(s) under 35 U.S.C. 112(2) and 112(1) set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Thurs, 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656